REMARKS

With the entry of this Response, Claims 1-2 and 11-28 are pending. Claims 3-10 have been canceled, Claims 1-2 have been amended, and Claims 11-28 have been added. No new matter is believed to be added by these amendments. Support for the new claims is found in the Specification of the published application (U.S. 2006/0252110 A1) as follows:

Claims 11-14 in at least paragraph [0033];

Claims 15-17 in at least paragraphs [0031], [0106], and [0123];

Claims 18-19 in at least paragraph [0030];

Claims 20-22 in at least paragraphs [0039] and [0044];

Claim 24 in at least paragraphs [0031], [0044], and [0045];

Claim 26 in at least paragraphs [0033], [0038], [0043], and [0045];

Claim 27 in at least paragraphs [0004] and [0040]; and

Claim 28 in at least paragraph [0033], [0038], [0043] and [0045].

In view of the following remarks, Applicants respectfully request reconsideration and allowance of the pending claims.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Office Action rejected Claims 1-3 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office Action makes the following statements:

- Claim 1 lacks antecedent basis for the recitation of "the absorbance value"
- Claim 2 lacks antecedent basis for the recitation of "a change" at line 4
- Claim 3 lacks antecedent basis for the recitation of "a change" at line 4
- Claim 2 is vague and indefinite in the recitation of "increased biliverdin concentration"
- Claim 3 is vague and indefinite in the recitation of "an above-normal biliverdin concentration"

According to the Office Action, the metes and bounds of these claims cannot be determined. To expedite the prosecution of these claims to allowance, Applicants have amended Claims 1-2 and have canceled Claim 3. Applicants submit that the amendments to Claims 1-2 and the cancellation of Claim 3 overcome this rejection. Applicants respectfully request that the Examiner withdraw this rejection and allow these claims.

REJECTIONS UNDER 35 U.S.C. § 103

The Office Action rejected Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yein *et al.* (U.S. Patent No. 5,783,407) (hereinafter Yein) in view of Falchuk (U.S. Patent No. 6,902,881) (hereinafter Falchuk), Lin *et al.* (U.S. Patent No. 5,284,940) (hereinafter Lin), and the DERWENT Abstract (AC No: 1987-173702) (hereinafter Abstract). Having reviewed these references, the Office Action states:

> it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to select a sample which comprises biliverdin from snakes or birds and further to add the enzyme, bilverdin reductase, in an assay disclosed by Yein et al because biliverdin is clearly disclosed to be in snake and bird species by Falchuk and Lin et clearly teach bilverdin reductase and DERWENT teaches that reductases are oxidizing enzymes.

(Office Action, p. 5). Applicants respectfully traverse this rejection to the extent that the rejection applies to the amended claims.

Under 35 U.S.C. § 103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires: (1) that there be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) that there be a reasonable expectation of success; and (3) that the prior art reference (or references when combined) teaches or suggests all of the claim limitations. (*See, e.g.*, M.P.E.P § 2143). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and cannot be based on Applicant's disclosure. (*See, e.g., In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Fine*, 87 F.2d 1071, 1074 (Fed. Cir. 1988)). Furthermore, rejections based on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be explicit analysis including some rational underpinning to support the legal conclusion of obviousness. (*K.S.R. Int'l Co. v. Teleflex, Inc.*, 550 U.S. 14 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). If the references do not teach each of the claimed elements, then a finding of obviousness fails.

Applicants respectfully submit that the cited references, whether alone or in combination with one another, fail to teach Applicants' currently claimed invention. Although Applicants direct comments to each of the references in turn, Applicants are aware that the rejection is made

with the combination of the references and note that this Response is not directed to the references individually.

The Office Action points to several citations in Yein, that in combination with other cited references, allegedly render Applicants' currently claimed invention obvious. Applicants respectfully submit that Yein, alone or in combination with the other cited references, fails to provide a teaching or suggestion of Applicants' currently claimed invention. The Office Action states that Yein teaches:

1. a method of determining/measuring biliverdin (col. 2, lines 20-21) concentration in a sample comprising contacting the sample (col. 2, line 24, e.g. tissue)

2. with an oxidizing enzyme (col. 2, lines 60-64),

3. measuring a change in absorbance within a range of 325 to about 750 nm (col. 6, lines 15-21, lines 27-30, lines 51-53) and

4. determining/measuring biliverdin concentration by comparing the absorbance values to a control or a standard curve (col. 7, lines 51-52 and lines 7).

(Office Action, p. 5). Applicants respectfully submit that Yeins fails to teach or suggest the measurement of a product species, such as biliverdin. Rather, Yein teaches an assay for detecting conjugated bilirubin by following the decrease in absorbance at 460 nm. This decrease in absorbance indicates the oxidation of conjugated bilirubin by bilirubin oxidase as well as the oxidation of biliverdin to a purple pigment (an unknown compound) by bilirubin oxidase.

The Office Action states that Yein recites that "the product species, the analyte or both can be detected." (*See, e.g.*, col. 2, lines 20-21). To the contrary, Yein teaches a limited assay that is designed to measure only a specific fraction (*i.e.*, conjugated bilirubin) of the total analyte (*i.e.*, conjugated bilirubin + unconjugated bilirubin) available in a sample. Yein states that when bilirubin is the analyte, the only form of bilirubin that can be assayed is conjugated bilirubin. Furthermore, as some amount of the analyte appears to be altered by "autocatalytic activity" prior to measurement of the analyte, Yein fails to measure substantially all of the analyte present. Consequently, Yein fails to teach measuring other fractions of bilirubin that are found naturally in a sample, such as unconjugated bilirubin. As unconjugated bilirubin is not oxidized by bilirubin oxidase, Yein teaches away from an assay that measures substantially all of the analyte present in a sample. (*See* col. 6, lines 29-30). Thus, Yein teaches an assay of a subset of the

analyte present in a sample, and that the analyte to be detected is not substantially all of the analyte present in the sample.

The Office Action states that Yein "clearly recognize[s] that each of biliverdin and bilirubin can be determined or measured based on absorbance values taken and compared with absorbance values on a standard curve or from a control sample." (Office Action, p. 6, citing to Yein, col. 2, lines 20-21). Applicants respectfully submit that, at best, Yein provides a teaching of an assay that measures the change to a compound as measured by the reduction of an absorbance value at a particular wavelength. Nevertheless, Yein fails to teach (1) determining the identity of one or more product species, (2) how any product species may be measured, (3) what wavelength to use to try to identify one or more product species, (4) what compounds to use to establish a standard curve, and (5) the quantity of the one or more product species produced by the oxidation of conjugated bilirubin. Rather, Yein requires the mixing of a sample containing an analyte with a stabilizing compound, incubating the mixture until the autocatalyzing activity has ceased, adding an enzyme, and measuring the change in light absorbance at a particular wavelength in a spectrophotometer. When the analyte is bilirubin, the sample is incubated until autocatalyzation of bilirubin ceases, bilirubin oxidase is added, and the decrease in absorption at 460 nm is monitored. (*See* Yein, col. 6, lines 54-57). Yein does not teach detecting any product species, or of any other wavelength for which a product species could be monitored. Therefore, Yein cannot be used as a teaching of detecting any product species of an enzymatic reaction, and particularly not the product species of bilirubin oxidase.

Yein teaches that the substrate for the enzyme bilirubin oxidase is bilirubin, and that bilirubin is oxidized to form biliverdin. It is known in the art that bilirubin oxidase will also oxidize biliverdin to a purple pigment. (*See* Tanaka, *Agric. Biol. Chem.* 49(3): 843-844 (herein "Tanaka"). Applicants enclose a copy of Tanaka with this Response. Yein teaches that the bilirubin oxidase of Tanaka is a preferred bilirubin oxidase. Because the assay of Yein only measures the decrease in absorbance at 460 nm, which is the absorbance wavelength for conjugated bilirubin, Yein can only measure the oxidation of conjugated bilirubin. Furthermore, in the Yein assay, bilirubin oxidase also oxidizes the biliverdin present naturally or formed during the autocatalytic or enzymatic activity. But Yein fails to provide a teaching or suggestion to determine the identity of the product species, of which at least two may be present in the Yein assay. Thus, contrary to the Office Action's assertion, Yein fails to teach "determining /

measuring biliverdin concentration by comparing the absorbance values to a control or a standard curve."

The Office Action states that "Since just as the enzyme reaction of bilirubin oxidase can be used to measure bilirubin by oxidizing bilirubin to biliverdin, the enzyme reaction of biliverdin reductase can be used to measure biliverdin by the conversion of biliverdin to bilirubin." However, the "enzyme reaction of bilirubin oxidase" as taught by Yein can only be used to measure a particular subset of bilirubin present in a sample – that is, conjugated bilirubin. Even then, Yein can only measure the subset of bilirubin that does not undergo autocatalytic activity. It is not a simple or obvious process to substitute one enzyme for another in an assay, to substitute one analyte for another, and to measure substantially all of the analyte in a sample. In short, Yein fails to support a rejection of the Applicants' currently pending claims. Yein, in combination with the other cited references, cannot provide a teaching or suggestion that renders Applicants' currently pending claims obvious.

According to the Office Action, Falchuk "teaches samples which comprise biliverdin, see col. 12, lines 36-41 and line 66. The sample is from an avian or reptilian species, note col. 27, line. 4." (Office Action, p. 5). The Office Action also states that "Falchuk teach[es] that samples of biliverdin are obtainable from avian or reptilian species and one having the knowledge in the art to measure change in absorbance to determine biliverdin would have been able to obtain the same from these species." (Office Action, p. 8). Applicants respectfully traverse the Office Action's interpretation of Falchuk.

Applicants respectfully submit that Falchuk is directed to methods and reagents for inhibiting cell growth or promoting cell differentiation comprising contacting the cell with a differeguline in a sufficient amount to inhibit cell proliferation or promote cell differentiation. (*See*, *e.g.*, Abstract). Falchuk describes differegulins as "master switch molecules [that] are the ones that act at the earliest, decisive steps in differentiation and are most likely to act on cancer cells to drive their differentiation forward." (col. 12, lines 20-23).

Falchuk fails to teach or suggest assays or the detection or treatment of avian or reptilian hepatic function. Applicants are uncertain as relevance of the Office Action's citation to Falchuk at col. 12, lines 36-41 and line 66 and at col. 27, line 4. For example, col. 12, lines 36-41 and line 66 of Falchuk disclose that differegulins are present in both mammals and non-mammals and that biliverdin appears to be a differegulin. When read in the context of the entire paragraph, col.

27, lines 4-6 disclose that progenitor cells can be harvested from embryonic, post-natal, juvenile, or adult neural tissue from fish, reptiles, birds, amphibians, or mammals, although mammals are the most preferred source for donor cells.

Applicants respectfully submit that Falchuk is directed to compounds and methods for regulating cell differentiation. Other than using the terms "reptiles," "birds," and "biliverdin," the cited portions of Falchuk fail to teach or suggest Applicants' currently claimed invention. Whether alone or in combination with other references, Falchuk fails to supplement the teachings missing from Yein to result in a teaching or suggestion of Applicants' currently claimed invention.

The Office Action cited Lin for the teaching "that biliverdin may be converted to bilirubin by the enzyme biliverdin reductase." (Office Action, p. 5 (citing col. 14, lines 58-60). Lin is directed to methods and compounds for the preparation of nucleic acid samples. (*See*, *e.g.*, Abstract). More specifically, Lin provides "a method to both isolate nucleic acid sequences from biological sources and to neutralize any agents that might inhibit further manipulation of the concentrated nucleic acid sequences." (Col. 7, ll. 56-61). When read in context, the cited portion discloses that, in an attempt to eliminate inhibition of polymerase by inhibitors, Lin contemplates the use of heme oxygenase to treat heme-type inhibitors. (Col. 14, ll. 47-60).

Applicants respectfully traverse the Office Action's statement that "it would have been obvious to replace the enzyme of Yein et al with the reductase enzyme of Lin et al in order to measure this compound." (Office Action, p. 8). Although Lin uses the term "biliverdin reductase," Lin does not teach or suggest use of the enzyme in an assay for analytes in a biological subject. The combination of Yein's assay and Lin's use of heme oxygenase to treat heme-type inhibitors would not provide a teaching or suggestion of Applicants' currently claimed invention. Additionally, Lin fails to provide a teaching that would cure the deficiencies of Yein and Falchuk such that the combination of Lin, Falchuk and Yein render Applicants' currently claimed invention obvious.

The Office Action states that the Derwent Abstract "teaches that reductase enzyme is an oxidizing enzyme." (Office Action, p. 5). The Office Action states that:

> one of ordinary skill in the art would have expected successful results for determining biliverdin concentration in a bird or snake sample using an enzyme reaction mixture of the sample and biliverdin reductase since the enzyme is well recognized to

> be an oxidizing enzyme and can convert biliverdin to bilirubin and oxidizing enzymes can also convert bilirubin to biliverdin.

(Office Action, p. 6). Applicants respectfully assert that in an effort to make the teaching of Yein more relevant, the Office Action misunderstands the enzymatic abilities of biliverdin reductase. The art characterizes biliverdin reductase as an oxidoreductase because it reduces biliverdin to bilirubin and oxidizes NADPH (or NADH) to NADP+ (or NAD+). Biliverdin reductase does not oxidase bilirubin or biliverdin. The Abstract fails to provide a teaching or suggestion of Applicants' currently claimed invention. Furthermore, when combined with the other cited references, the Abstract fails to supplement the deficiencies of the combination of Yein, Falchuk, and Lin. Like Yein, Falchuk, and Lin, the Abstract fails to support a rejection of obviousness for the currently amended claims.

The Office Action has not provided a combination of references that teach or suggest all the elements of the currently claimed invention. Also, the Office Action has not provided the motivation required to combine such references. The Examiner has the burden of providing a rationale from the prior art for making the specific claimed modification or combination. The *KSR* Court confirmed that it is legally insufficient to merely point to the various recited elements. Instead, the Office must identify the basis for the alleged modification or combination by one of ordinary skill to arrive at the claimed invention.

> As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

(*KSR* at *37-*38). Absent this explicit reasoning to support the basis for the modification or combination, the alleged modification or combination cannot support a *prima facie* obviousness rejection.

Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness. The primary reference, Yein, is directed to an assay for a subset fraction of an analyte, and that analyte is not found in the subjects that are the focus of Applicants' currently claimed invention. The cited references fails to provide a teaching that supplements the teachings missing from Yein to yield Applicants' currently claimed invention. Furthermore, other than Applicants' specification, the Office Action has failed to provide evidence of motivation to combine the cited references. A person having ordinary skill in the art would not look to Yein for guidance nor combine Yein with Falchuk, Lin, and the Abstract to arrive at Applicants' currently claimed invention. For at least the reasons stated above, whether considered individually, or in combination with one another, the cited references fail to provide a teaching or suggestion that results in Applicants' currently claimed invention. The combination of these references fails to render Applicants' currently pending claims obvious. Applicants respectfully request that the Examiner withdraw this rejection and allow all of the pending claims.

CONCLUSION

The foregoing is a complete response to the Office Action dated May 29, 2009. For at least the reasons provided above, Applicants respectfully request allowance of all of the pending claims. Early and favorable consideration is solicited. If a telephone conversation would expedite the prosecution of these claims to issuance, then Applicants' representative invites and encourages the Examiner to contact the Applicants' representative at the telephone number listed below.

Applicants file this Amendment and Response solely to facilitate prosecution. As such, Applicants reserve the right to pursue claims of broader or similar scope as originally filed in a continuation application or other application after allowance of the present application. Applicants do not concede that the current or past rejections are correct and reserve the right to challenge such rejections later in prosecution or on appeal. Accordingly, any amendment, argument, or claim cancellation is not to be construed as abandonment or disclaimer of subject matter. Because certain of the current amendments may include broadening amendments, Applicants respectfully request the Examiner to revisit any previously reviewed references cited in this Application to further ensure that the currently pending claims remain patentable over any previously reviewed references.

Applicants enclose a Petition for a Two-Month Extension of Time for and a Credit Card payment in the amount of $245.00, representing the small entity fee pursuant to 37 C.F.R. § 1.17(a)(2) for a two-month Extension of Time. Applicants believe that this is the correct amount due; however, Applicant authorizes the Commissioner to charge to Deposit Account No. 14-0629 any additional fees that may be required, or to credit to the same account any overpayment of fees.

Respectfully submitted,

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APPENDIX A

Pursuant to 37 C.F.R. § 1.121(b)(1)(ii), below is a marked-up version of replacement paragraph [0031].

> [0031] As mentioned above, ~~bilirubin~~ biliverdin reductase is an enzyme responsible for the conversion of biliverdin to bilirubin. Therefore, by contacting biological samples with biliverdin reductase, any biliverdin present in the sample should be converted to bilirubin, thus allowing one of skill in the art to measure the amount of biliverdin present in the sample by measuring the change in absorbance at about 325 to about 750 nm. For example, wavelengths of about 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650,[[.]] 675, 700, 725 and 750 can be utilized. One of skill in the art can utilize any wavelength between about 325 nm and 750 nm that results in changes in absorbance corresponding to the measurement of biliverdin concentration or bilirubin production. For instance, as set forth in the Examples herein, at certain wavelengths, one of skill in the art will observe an increase in absorption that corresponds to increased bilirubin production. At other wavelengths, one of skill in the art will observe decreased absorption corresponding to ~~increased~~ decreased biliverdin concentrations. Biliverdin reductase can be obtained from commercial sources such as ICN Biochemicals or the enzyme can be cloned and produced by standard recombinant methods as described in the Examples herein. The biliverdin reductase can be from rat, mouse, human or other mammalian origin. One of skill in the art can determine the specific activity of a recombinant biliverdin reductase preparation as well as the concentration of biliverdin reductase necessary for conversion of biliverdin to bilirubin. The preparation can be such that no other bacterial proteins or other contaminants are present in the preparation or the preparation can be purified such that all or most bacterial proteins are removed.